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Applicant	:	Liu et al.	Art Unit	:	1647
Serial No.	:	09/805,449	Examiner	:	Landsman, R
Filed	:	03/13/2001			
Title	:	METHODS OF MODULATING CELL MIGRATION USING GALECTIN-3			

Assistant Commissioner of Patents
Washington, DC 20231

DECLARATION OF DR. FU-TONG LIU
UNDER 37 C.F.R. §1.132

Sir:

1. I, Fu-Tong LIU, M.D., Ph.D., declare and say I am a resident of Davis, California. My residence address is: 2963 Audubon Circle, Davis, CA 95616.
2. I received Bachelor of Science degree in Chemistry from National Taiwan University, in 1970. I received a Doctor of Philosophy degree in Chemistry from the University of Chicago in 1976. I received a Medical Doctor degree in 1987 from the University of Miami, School of Medicine. I am currently Professor and Chair of Department of Dermatology at University of California, Davis, School of Medicine. My curriculum vitae is attached, which reflects my expertise in the areas of allergy, dermatology, immunology, glycobiology and molecular biology.
3. I am an inventor of the subject matter claimed in United States Patent Application Serial No. 09/805,449, filed March 13, 2001.
4. I have reviewed the claims that are presently under examination.
5. I am the first listed author of Liu *et al.*, Biochemistry 35:6073 (1996), hereinafter referred to as Exhibit 1.
6. I submit this declaration to state that one or more of the antibodies described in Exhibit 1 is expected to stimulate cell migration in accordance with the claimed methods.

7. The studies in Exhibit 1 were performed by me, under my direction or by the listed co-authors. I therefore have an intimate understanding of the data presented in Exhibit 1.

8. The studies described in Exhibit 1 concern seven antibodies that bind galectin-3. Three of these antibodies, A3A12, B3A12 and C1C2 were demonstrated to activate galectin-3, as assessed by enhanced galectin-3 binding to IgE and enhanced galectin-3 hemagluttinating activity. One of these antibodies, A3A12, significantly enhanced superoxide (SO) production of neutrophils.

9. Based on the data in Exhibit 1 and my expertise in the fields of immunology and molecular biology, I conclude that at least one of the seven antibodies described in Exhibit 1 is expected to stimulate cell migration in accordance with the claimed methods.

10. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title XVIII of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Oct 7, 2003
Date

Dr. FU-TONG LIU, MD, PhD.

EXHIBIT "1"

Modulation of Functional Properties of Galectin-3 by Monoclonal Antibodies Binding to the Non-Lectin Domains†

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ABSTRACT: Galectin-3 is a member of a newly defined family of animal lectins, which is composed of three domains: a small amino-terminal domain, a domain containing repeating elements, and a carboxyl-terminal domain containing the carbohydrate-recognition site. Various functions have been described or proposed for this lectin, and it appears that galectin-3 has diverse roles. Murine monoclonal antibodies (MAbs) have been generated from mice hyperimmunized with recombinant human galectin-3 or galectin-3C (the carboxyl-terminal domain), and seven MAbs have been characterized in detail. All MAbs generated against the intact galectin-3 recognize the amino-terminal region of the molecule, as demonstrated by ELISA and immunoblotting using recombinant galectin-3C and galectin-3NR, which contains the amino-terminal domain and all the repeating elements. Their epitopes were all found to be within the first 45 amino acids of galectin-3, as determined by using galectin-3 mutants with a truncated amino-terminal region. However, these MAbs were found to profoundly modulate the lectin activities of galectin-3. The MAb B2C10 inhibited (i) the binding of ^{125}I-labeled galectin-3 to IgE coated on microtiter plates; (ii) the galectin-3's hemagglutination activity; and (iii) galectin-3-induced superoxide production by human neutrophils. Other MAbs, especially A3A12, caused marked potentiation of these activities. The results support our model that the lectin function of galectin-3 is influenced by protein homodimerization resulting from self-association of the amino-terminal region of the molecule. The potentiating activities of some MAbs are probably due to facilitation of dimerization of galectin-3, and the inhibitory activity of MAb B2C10 is probably the result of its disruption of the self-association process.

Galectins are a newly defined family of animal lectins (Barondes et al., 1994a,b), with the most extensively studied members being the M_r 14 000 (galectin-1) and the M_r 30 000 (galectin-3) proteins. The latter has previously been designated variously as IgE-binding protine (BP),[1] for its IgE-binding activity (Liu et al., 1985; Albrandt et al., 1987; Robertson et al., 1990), Mac-2, a macrophage surface antigen (Cherayil et al., 1989, 1990), CBP35 (Roff & Wang, 1983; Jia & Wang, 1988), CBP30 (Mehul et al., 1994), L-29 (Leffler et al., 1989), and L-34 (Raz et al., 1989, 1991). Galectin-3 consists of three domains: the amino-terminal half is made of a small N-terminal domain and repeating elements, and the carboxyl-terminal half contains the carbohydrate-binding site (Herrmann et al., 1993).

The function of galectin-3 appears to be diverse. The expression of this lectin was found to be markedly elevated in proliferating fibroblasts, and, moreover, it is concentrated in the nucleus in these proliferating cells (Moutsatsos et al., 1987), suggesting that galectin-3 may be a component of a cell-growth regulating system. More recently, galectin-3 has been identified as a factor in pre-mRNA splicing (Dagher et al., 1995). This lectin has been associated with tumor transformation and metastasis (Raz et al., 1990; Castronovo et al., 1992; Lotz et al., 1993; Irimura et al., 1991). Galectin-3 is also likely to function extracellularly, as the protein is found on the cell surfaces (Frigeri & Liu, 1992) and is secreted (Cherayil et al., 1989; Lindstedt et al., 1993; Sato et al., 1993). It was found to be a major non-integrin laminin-binding protein, and thus its role in cell adhesion to basement membranes has been proposed (Woo et al., 1990). Galectin-3 was shown to recognize cell surface glycoproteins on various cell types and is capable of activating cells including mast cells, neutrophils, and monocytes (Frigeri et al., 1993; Yamaoka et al., 1995; Liu et al., 1995), and a picture is emerging that this protein may be a broad-spectrum biological response modifier (Liu, 1993).

One unusual structural feature of galectin-3 that is unique among all galectins is the presence of highly conserved tyrosine, proline, and glycine-rich tandem repeats in the amino-terminal half of the molecule. We have previously

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[1] Abbreviations: BSA, bovine serum albumin; BP, IgE-binding protein (galectin-3); galectin-3C, carboxyl-terminal carbohydrate-binding domain of galectin-3; galectin-3NR, amino-terminal domain and repeating elements of galectin-3; ELISA, enzyme-linked immunosorbent assay; FITC, fluorescein isothiocyanate; GST, glutathione *S*-transferase; hu galectin-3, human galectin-3; MAb, monoclonal antibody; PBS, phosphate-buffered saline; PCR, polymerase chain reaction.

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shown positive cooperativity in the binding of galectin-3 to IgE coated on microtiter wells and proposed that this protein has a tendency to self-associate through intermolecular interactions involving the amino-terminal region of the molecule (Hsu et al., 1992). Similar positive cooperativity has been noted in binding of this lectin to laminin (Massa et al., 1993), and a recombinant polypeptide containing the N-terminal domain and the repeating elements has been found to efficiently self-assemble into oligometric species (Mehul et al., 1994). This self-association process was also believed to be operative in the binding of galectin-3 to mammalian cell surfaces, and the ability of this lectin to activate various cells was thought to be critically dependent on its noncovalent dimerization or oligomerization (Frigeri et al., 1993; Yamaoka et al., 1995; Liu, 1993).

Polyclonal antibodies to galectin-3 have been used extensively for the studies of this lectin. Although a monoclonal antibody (MAb) made against mouse galectin-3 (Mac-2) is available (Ho & Springer, 1982), for further structural and functional analyses of galectin-3 a panel of MAbs recognizing the protein from different species and different regions of the protein should be valuable. Here, we report the generation of a number of MAbs against galectin-3 that are useful for detection of this lectin in various immunoassay procedures. Interestingly, all MAbs made against the intact galectin-3 recognized the amino-terminal region of the molecule. However, many either inhibited or potentiated the lectin functionality of galectin-3 which is associated with the carboxyl-terminal, carbohydrate-recognition domain.

MATERIALS AND METHODS

Reagents. Recombinant human galectin-3 (hu galectin-3) (Hsu et al., 1992), the carboxyl-terminal domain of human galectin-3 (hu galectin-3C) (Hsu et al., 1992), recombinant rat galectin-3 (Frigeri et al., 1990), and mouse monoclonal anti-dinitrophenyl IgE and IgG_1 (Liu et al., 1980) were prepared as described previously. Recombinant mouse galectin-3 (CBP 35) was kindly provided by Dr. J. L. Wang, Michigan State University. Lactosyl-Sepharose 4B was prepared as described (Levi & Teichberg, 1981). Unless otherwise stated, all other reagents were from Sigma Chemical Co. (St. Louis, MO). ^{125}I-Labeled hu galectin-3 was prepared by reacting 10 μg of the protein with 0.5 mCi of $Na^{125}I$ in the presence of chloramine-T (McConahey & Dixon, 1966). Labeling of hu galectin-3 by fluorescein isothiocyanate (FITC) was performed as described (Coligan et al., 1992).

Preparation of Hybridomas. (1) Immunization. Balb/c mice were immunized with 20 μg of recombinant hu galectin-3, or galectin-3C in complete Freund's adjuvant (DIFCO) injected subcutaneously. The mice were boosted 1 month later with 10 μg of hu galectin-3 or galectin-3C in incomplete Freund's adjuvant injected subcutaneously. The mice were bled 7 days later, and sera were assayed for the anti-galectin-3 antibody titer by ELISA as described below. Two mice with the highest titers were boosted daily for 3 consecutive days with 10 μg of hu galectin-3 or galectin-3C in incomplete Freund's adjuvant injected intraperitoneally. One day after the last dose, the animals were sacrificed, and the spleens were harvested for fusion.

(2) Construction of Hybridomas. The spleen cells were fused with a myeloma cell line (SP2/0) (Shulman et al., 1978), and the fused cells were subcultured, as described previously (Liu et al., 1980). Hybridomas secreting anti-galectin-3 antibody were detected by ELISA as described below, positive clones were subcloned, and the subclones secreting the desired antibodies were again screened by ELISA. The isotypes of MAbs were determined with culture supernatants from subclones by using an immunoglobulin isotyping kit from Pharmingen (San Diego, CA).

Purification of Monoclona Anti-Galectin-3 Antibodies. (1) Generation of Ascites Fluids Containing the MAbs. Hybridoma cells were injected intraperitoneally into pristane-primed mice (10^6 cells per mouse), and the ascites fluids developed were harvested by standard procedures.

(2) Purification of Immunoglobulins from the Ascites. The ascites fluids were passed through glass wool and then mixed with Biocryl BPA1000 (Tosohaas, Montgomeryville, PA) at 1% final concentration for 0.5 h at 25 °C. The mixture was spun at 7800*g* for 15 min at room temperature. The supernatant was collected, and then 2.5 volume of 25% sodium sulfate was added dropwise while stirring. The mixture was spun at 31200*g* for 15 min at 25 °C, and the pellet was resuspended in 20 mM Tris-HCl, 60 mM NaCl, pH 8.0 (buffer A), and dialyzed against buffer A at 4 °C. The solution was spun at 31200*g* for 15 min at 4 °C, and the supernatant was loaded onto a Q-Sepharose column (Pharmacia, Piscataway, NJ). The column was washed extensively with buffer A, and the bound protein was eluted with 20 mM Tris-HCl, 200 mM NaCl, pH 8.0. The concentration of the eluted protein was determined by the absorbance at 280 nm.

(3) Preparation of Fab'. Fab' for one of the MAbs (A3A12) was obtained by digestion with pepsin followed by reduction and alkylation as described (Harlow & Lane, 1988). The resulting mixture was anlayzed with SDS–PAGE and found to display the patterns expected for Fab' and Fc under reducing and nonreducing conditions. The preparation was used without further purification.

Generation of Galectin-3 Mutants with Selected Deletions in the Amino-Terminal Region of the Molecule. Plasmids carrying a series of 5' deletions of the galectin-3 cDNA were constructed using primer-directed mutagenesis as follows: downstream primer, 5'-GCTCCATGGTAGGCGCCTG-GAGG-3', was common to all PCR reactions and contained the internal *Nco*I site at position 207 in the galectin-3 cDNA sequence (Robertson et al., 1990). Upstream primers were synthesized to introduce an *Nco*I site which included an ATG initiating codon at positions 106, 143, and 170: for galectin-3(Δ1−36), 5'-GGGGCCATGGGCTACCCAGGGG-3'; for galectin-3(Δ1−45), TATCCCATGGCCTACCCCGGGCAG; and for galectin-3(Δ1−54), 5'-CCCCCCATGGCTTATC-CTGGACAG-3'. pDH BP (Hsu et al., 1992) linearized with *Hin*dIII was used as the template, and PCR was carried out using standard procedures. PCR products of expected sizes (104, 77, and 50 bp) were isolated after agarose gel electrophoresis, digested with *Nco*I, and ligated into *Nco*I-digested pDH BP. The plasmids were used to transform *E. coli*. Clones expressing the desired products were isolated and expanded, and the mutant galectin-3 proteins were purified using lactosyl-Sepharose 4B as described (Hsu et al., 1992). The mutant galectin-3 containing an internal delection in the amino-terminal region, galectin-3(Δ19−58), was obtained as a side product in a primer-directed mutagenesis experiment, similar to that described above. The

upstream primer used was 5′-CAGACCATGGCAGACAATTTTTCGCTC-3′, and the downstream primer used was the same as described above for other deletion mutants. For all mutants, the sequence of the regions obtained by PCR was verified by nucleotide sequencing.

Generation of a Fusion Protein Containing the Galectin-3 Amino-Terminal Domain and Repeating Elements Linked to Glutathione S-Transferase (GST−Galectin-3NR). A plasmid containing the GST−galectin-3NR fusion DNA was made by using PCR amplification of the 5′-portion of the galectin-3 cDNA. Two oligonucleotides, 5′-AGCGGATCCTGGCAGACAATTTTTCG-3′ and 5′-CCACGGAGCGTACGACATTTCTTAAGAC-3′, were used as the upstream and downstream primers, respectively. These primers were designed to introduce a *Bam*HI site within the upstream primer and an *Eco*RI site and a termination codon within the downstream primer. They were then used to amplify a region of galectin-3 cDNA coding for a 131 amino acid long amino-terminal region of galectin-3 using pDH BP as the template. The PCR product was purified by agarose gel electrophoresis, digested with *Bam*HI and *Eco*RI, and ligated into *Bam*HI/*Eco*RI-digested vector pGEX-5X-3 (Pharmacia) containing the GST cDNA flanked by a factor Xa cleavage site. The plasmid was used to transform *E. coli*, and the fusion protein was isolated by affinity purification of bacterial lysates with glutathione−agarose (Smith & Johnson, 1988).

Enzyme-Linked Immunosorbent Assay (ELISA) for Detecting Anti-Galectin-3 Antibody. Ninety-six-well microtiter plates were coated with either 2 μg/mL recombinant hu galectin-3 (50 μL/well) or 10 μg/mL hu galectin-3C overnight at 4 °C. The wells were then blocked with 1% bovine serum albumin (BSA) in phosphate-buffered saline (PBS) (200 μL/well) for 2 h at room temperature. Fifty microliters of the hybridoma supernatants or serial dilutions of the mouse sera in 1% BSA and 0.05% Tween-20 contained in PBS were added to the wells, and the plates were incubated for 3 h at 4 °C. The bound antibodies were detected by goat anti-mouse IgG-horseradish peroxidase (Zymed, San Francisco, CA; diluted 1:2000 in the same diluent, 50 μL/well) followed by the substrate ABTS [2,2′-azinobis(3-ethylbenzthiazoline-6-sulfonic acid)]. The plates were washed with PBS between each step. The color developed was read on a Titertek Multiscan spectrophotometer at 405 nm.

Immunoblot Analysis. For detection of galectin-3, galectin-3C, galectin-3NR, and galectin-3 mutants by MAbs, the purified proteins (20 ng/lane) were separated by 12% SDS−PAGE (Laemmli, 1970) and transferred to poly(vinylidene difluoride) membranes (Immobilon P, Millipore, Bedford, MA). The membranes were then incubated with MAbs (0.5 μg/mL), followed by alkaline phosphatase-labeled goat anti-mouse IgG (Zymed 1:8000 dilution). Chemiluminescent detection using a Tropix kit (Bedford, MA) was employed for visualization.

Assays for the Effects of the Anti-Galectin-3 MAbs on Galectin-3 Activity. (1) Binding to IgE: Radioligand Binding Assay. The ability of MAbs to inhibit the binding of radiolabeled galectin-3 to IgE was evaluated by using a previously reported assay (Hsu et al., 1992; Frigeri et al., 1990). Briefly, microtiter plates were coated with mouse monoclonal IgE, and ^{125}I-labeled hu galectin-3 (1 10^6 cpm/well) was added to each well together with (a) serially diluted MAbs; (b) 50 mM thiodigalactoside; or (c) buffer alone. An additional control experiment was performed with Fab′ fragments of one MAb, A3A12. The diluent used was 1% BSA/0.05% Tween 20/PBS. The plates were incubated at 4 °C for 4 h and washed extensively, and then individual wells were counted for radioactivity.

(2) Hemagglutination. Human blood from healthy donors with blood group A was prepared for the hemagglutination assay as described (Hsu et al., 1992). Ten microliters of serially diluted hu galectin-3 and 25 μL of a MAb (1−200 μg/mL) were added to microtiter plates with U-bottom wells. To each well was added 25 μL of resuspended human blood cells (2.5%), and the plates were incubated at 25 °C for 30 min, and the end points were determined visually by the settling pattern.

(3) Fluorescence Flow Cytometry. For testing the effect of MAbs on the binding of galectin-3 to cell surfaces, FITC-labeled hu galectin-3 was incubated with HeLa cells in the presence or absence of specific or isotype-matched control antibodies. After incubation, the cells were washed and then analyzed on a FACScan (Becton-Dickson), according to a published protocol (Segal et al., 1987).

(4) Stimulation of Superoxide Production by Neutrophils. The procedure for measuring galectin-3-stimulated superoxide production from human neutrophils is essentially as described based on the reduction of cytochrome *c* by superoxide anion (Yamaoka et al., 1995). For testing the effect of the MAbs, neutrophils were treated with galectin-3 (50 μg/mL) in the absence or presence of anti-galectin-3 MAb or an isotype-matched control antibody.

RESULTS

Generation of Anti-Galectin-3 MAbs. Twenty clones secreting anti-galectin-3 MAbs were obtained in the first hybridoma experiment from mice hyperimmunized with recombinant hu galectin-3. All these clones were subcloned, and the secreted MAbs purified from the ascites fluids were studied in various assays described below. MAbs from six different clones that were deemed most useful were more extensively characterized. It appeared that all the MAbs produced from the first experiment recognized the amino-terminal region of galectin-3, as they did not bind galectin-3C in either ELISA or immunoblot analysis (see below). Since MAbs binding to the carboxyl-terminal lectin domain were also desirable, another hybridoma experiment was performed using spleen cells from mice immunized with hu galectin-3C. Five clones were obtained and analyzed, and one of them (14D3) was more extensively characterized.

The seven MAbs described in detail herein are listed in Table 1. All are IgG_1 with light chains. In ELISA, two MAbs (A1D6 and A3A12) cross-reacted with rat galectin-3, and five (A3A12, B2C10, B3A12, C1C2, and B1A7) cross-reacted with the mouse counterpart. Some of the MAbs purified from the ascites were found to be contaminated by galectin-3 (by immunoblot analysis, data not shown), most likely representing the mouse endogenous galectin-3, present in the ascites fluids, that forms complexes with the MAbs. The contaminating galectin-3 could be removed by repeated adsorption with lactosyl-Sepharose 4B.

Mapping of Epitopes Recognized by the MAbs. In both ELISA and immunoblot analysis, all MAbs generated from mice immunized with the intact galectin-3 bound galectin-3 but not galectin-3C, and those made against galectin-3C bound both galectin-3 and galectin-3C (data not shown). The

Table 1: Summary of Characterization of Anti-Galectin-3 MAbs

designation[a]	reactivity to hu/rat/mu galectin-3[b]	effect on galectin-3 activity[c]		reactivity to galectin-3 mutants[e]			
		hemagglutination	binding to IgE	Δ1−36	Δ1−45	Δ1−54	Δ19−58
A1D6	+/+/−	P	I/P[d]	+	−	−	−
A3A12	+/+/+	P	P	+	−	−	+
B1A7	+/−/+	P	P	−	−	−	+
B2C10	+/−/+	I	I	−	−	−	+
B3A12	+/−/+	P	P	−	−	−	+
C1C2	+/−/+	P	P	ND[f]	ND	ND	ND
14D3	+/−/−	N	N	+	+	+	+

[a] 14D3 was generated from mice immunized with galectin-3C; other MAbs were generated from mice immunized with the intact galectin-3. [b] Determined by ELISA and immunoblot analysis (hu, human; mu, murine). [c] P, potentiation; I, inhibition; N, no effect. [d] Dependent on the concentration of galectin-3 used. [e] Determined by immunoblot analysis (see Figure 1). [f] ND, not done.

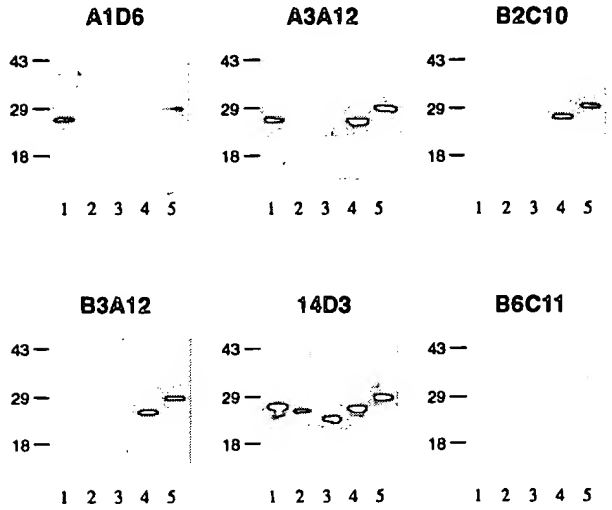

FIGURE 1: Immunoblot analysis of the reactivity of MAbs to galectin-3 mutants containing a truncated amino-terminal domain. The recognition of galectin-3 mutants by a panel of MAbs was determined by immunoblot analysis. The monoclonal antibodies are indicated at the top of each panel, and the mutant proteins indicated at the bottom of each panel are (1) Δ1−36, (2) Δ1−45, (3) Δ1−54, (4) Δ19−58, and (5) wild type. The molecular weights (10^{-3}) of the markers are indicated on the left margin.

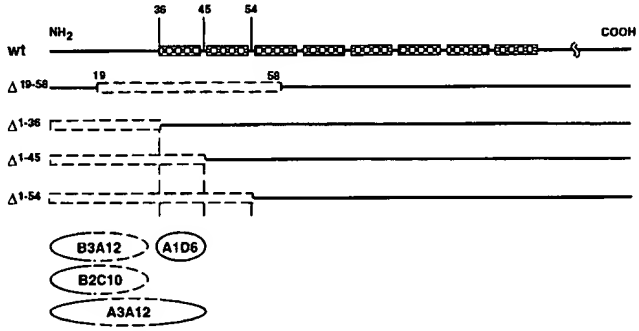

FIGURE 2: Schematic diagram of galectin-3 mutants and epitopes recognized by MAbs. The top line depicts the wild-type galectin-3; each of the checker bars represents one repeat sequence containing the nine amino acids as defined in Robertson et al. (1990). The open bar for each mutant indicates the deleted part in these mutants. The ovals at the bottom correspond to the areas in which the epitopes for the MAbs reside, with dashed lines indicating regions that cannot be excluded as epitopes. Numbers provide positional information in the sequence of the wild-type galectin-3.

recognition of the amino-terminal domain and the repeating elements by the MAbs was tested using a fusion protein containing galectin-3NR linked to glutathione *S*-transferase (GST). MAbs made against the intact galectin-3 (A3A12, B2C10, and A1D6) bound galectin-3NR, while that made against galectin-3C (14D3) did not, as expected (data not shown).

To further define the epitopes recognized by the MAbs, the reactivity of each MAb to galectin-3 mutants with a truncated amino-terminal region was determined by immunoblot. Mutants arising from deletion of 36, 45, and 54 amino acids from the amino-terminal region, i.e., galectin-3(Δ1−36), galectin-3(Δ1−45), and galectin-3(Δ1−54), respectively, were used. In addition, a mutant with an internal deletion of amino acids 19−58, galectin-3(Δ19−58), was included. The results of the immunoblot analysis are shown in Figure 1, and the pattern of reactivity of each MAb against a panel of mutants is summarized in Table 1. MAbs made against the intact galectin-3 exhibited varying patterns of recognition of various mutants. As expected, the MAb made against galectin-3C (14D3) recognized all mutants, while the control MAb (B6C11) did not bind any of them. An analysis of the pattern of recognition by each MAb allowed the conclusion that the epitopes for MAbs B2C10 and B3A12 reside within the first 18 amino acids and that the MAb A1D6 epitope is contained in the region between amino acids 36 and 45. MAb A3A12 exhibited anomalous reactivity in that this MAb appears to recognize independently regions present in Δ36−58 (amino acids 1−18) and in Δ1−36 (amino acids 36−45) (see Figure 2).

Effects of Anti-Galectin-3 Monoclonal Antibodies on the Activities of Galectin-3. (1) Effect on Galectin-3 Binding to IgE. The effect of MAbs on the binding of galectin-3 to IgE was determined by a solid-phase radioligand binding assay. First, radiolabeled galectin-3 alone with no added unlabeled galectin-3 was used (Figure 3A). Most MAbs potentiated the binding at lower concentrations, with MAbs A3A12, B3A12, and C1C2 increasing by almost 3-fold the binding of radiolabel to IgE, as compared to the binding in the absence of the MAbs. The potentiating effect of the MAbs plateaued at higher concentrations, and MAbs A1D6 and B1A7 then showed partial inhibition of the binding. MAb B2C10 is unique in that it exhibited clear inhibition of the binding at all concentrations used (1−100 μg/mL). Next, radiolabeled galectin-3 mixed with unlabeled galectin-3 at 25 μg/mL was used (Figure 3B). Similar results were obtained in that MAbs A3A12, B3A12, and C1C2 potentiated the binding, while A1D6 and B2C10 inhibited the binding, all in a dose-dependent fashion. Over a 5-fold increase in the binding was promoted by MAb A3A12, and nearly complete inhibition was achieved with MAb B2C10 at higher concentrations. None of the MAbs raised against galectin-3C had any detectable effect. In a control experiment (inset to Figure 3A), a preparation of the Fab′ fragment of A3A12 showed negligible enhancement of galectin-3 binding com-

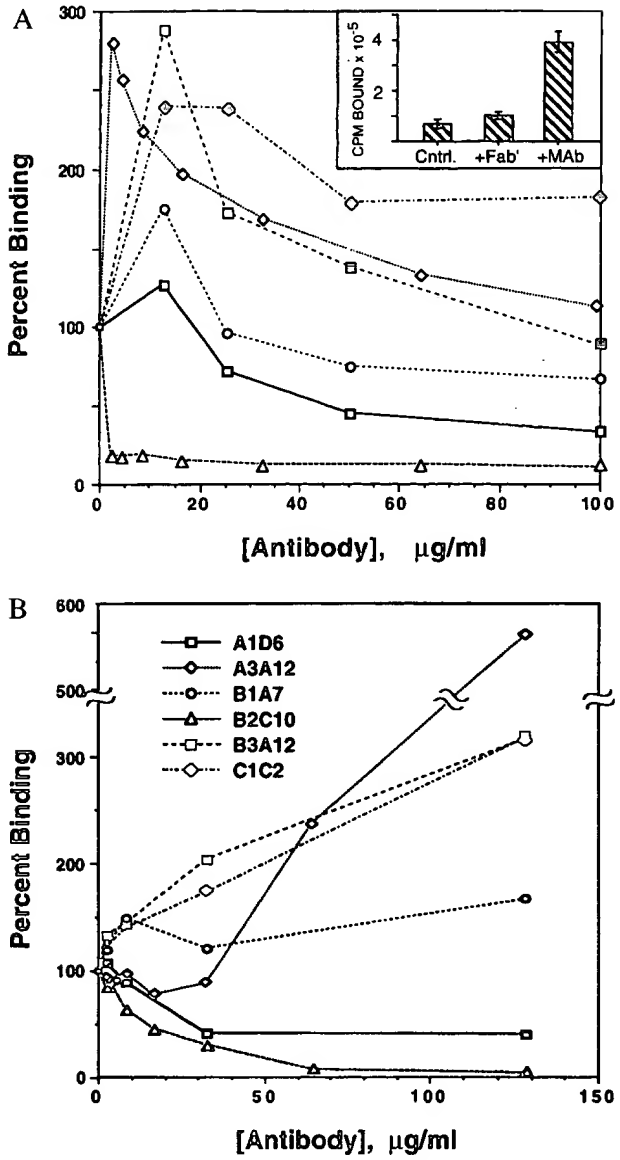

FIGURE 3: Effect of anti-galectin-3 MAbs on the binding of radiolabeled galectin-3 to IgE. Binding of ^{125}I-labeled hu galectin-3 to mouse monoclonal IgE was performed as described under Materials and Methods. For panel A, radiolabeled galectin-3 alone was used, and for panel B, radiolabeled hu galectin-3 plus 25 μg/mL unlabeled galectin-3 was used. Data represent means of triplicate determinations. Data point symbols for the various MAbs in panel A are identical to those indicated in panel B. The inset to panel A shows a control experiment comparing the effect of MAb A3A12 with its corresponding Fab′ fragment. Radiolabeled galectin-3 was used alone ("Cntrl."), with 2 μg/mL Fab′ ("Fab′"), or with MAb A3A12 ("MAb"). Data represent means of triplicate determinations. Similar results were obtained in two separate experiments.

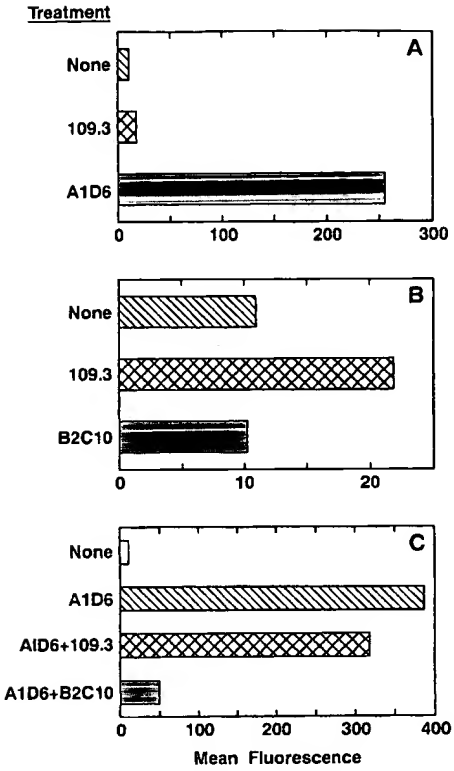

FIGURE 4: Effect of anti-galectin-3 MAbs on the binding of galectin-3 to the cell surface. HeLa cells (1 10^6) were incubated with FITC-labeled hu galectin-3 (10 μg/mL) in various conditions, and the intensity of cell surface fluorescence was assessed by flow cytometry. (Panel A) The cells were treated with fluorescent-labeled galectin-3 (10 μg/mL) either alone or together with MAb A1D6 or control MAb (20 μg/mL). (Panel B) The cells were treated with the fluorescent-labeled galectin-3 (10 μg/mL) either alone or together with MAb B2C10 or control MAb (50 μg/mL). (Panel C) The cells were treated with the fluorescent-labeled galectin-3 (10 μg/mL) and MAb A1D6 alone or together with MAb B2C10 or control MAb (50 μg/mL). Similar results were obtained in two separate experiments.

pared with galectin-3 alone, indicating that the observed enhancement is attributable to the divalence of the MAb. This small enhancement was probably attributable to trace amounts of divalent MAb present in the unpurified Fab′ preparation. An ELISA performed using galectin-3-coated microtiter plates, with the horseradish peroxidase conjugate of rabbit anti-mouse IgG as the detecting antibody, showed that A3A12 Fab′ was active in binding to galectin-3 (data not shown).

(2) Effect on the Hemagluttination Activity of Galectin-3. One of the characteristic properties of galectin-3 is its ability to agglutinate erythrocytes. The effects of MAbs on this activity were assessed. Most MAbs potentiated the hemagglutination activity of galectin-3 on human erythrocytes (Table 1). The potentiating activity was most pronounced with MAb A3A12, which enhanced the activity of galectin-3 over 10-fold: In its presence (1 μg/mL), galectin-3 caused hemagglutination at 0.25 μg/mL, whereas the hemagglutination titer of galectin-3 alone is typically 4 μg/mL. The MAb B2C10 inhibited the hemagglutination activity of galectin-3. A concentration of 8 μg/mL galectin-3 was required to cause hemagglutination in the presence of 25 μg/mL of this MAb, as compared to 4 μg/mL in its absence. None of the MAbs caused hemagglutination by themselves.

(3) Effect of Binding of Galectin-3 to the Cell Surface. Galectin-3 has been shown to bind to glycoconjugates on the cell surface of various cell types. The effect of the MAbs on the binding of galectin-3 to the cell surface was next assessed by fluorescence flow cytometry. As shown in Figure 4, panel A, MAb A1D6 caused marked potentiation of FITC-labeled galectin-3 binding to the surface of HeLa cells, while an isotype-matched irrelevant antibody (anti-DNP IgG_1, 109.3) did not have a significant effect. In contrast, MAb B2C10 had no apparent effect on the binding of FITC-labeled galectin-3 to the cells. However, MAb B2C10 did appear to have an inhibitory effect when a comparison was made between this MAb and a control, isotype-matched monoclonal antibody (panel B). The MAb

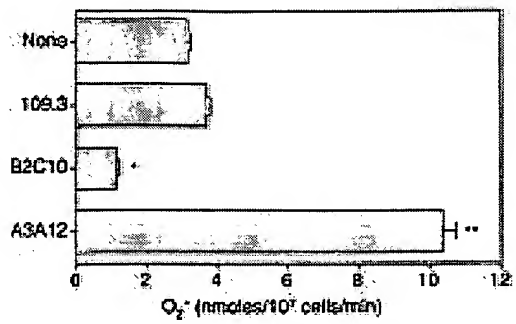

FIGURE 5: Effect of anti-galectin-3 MAbs on the galectin-3-induced superoxide production by human neutrophil. Human neutrophils (2.5 10^6 mL) in 0.25 mL of phosphate-buffered saline (pH 7.4) containing 0.5 mM $MgCl_2$, 1.1 mM $CaCl_2$, 7.5 mM glucose, 75 μM cytochrome *c*, and 6 μg/mL cytochalasin B were incubated for 5 min at 37 °C in the wells of a 96-well microtiter plate. The control wells also contained superoxide dismutase (60 μg/mL). To each well was added recombinant human galectin-3 (50 μg/mL) either alone or together with mAb A3A12, B2C10, or control antibody 109.3 (all at 100 μg/mL), after the mixtures were first incubated at room temperature for 10 min. The absorbance change at 550 nm was monitored with a kinetic microplate reader, and the readings were converted to the rate of O_2^- generation. The data represent means ± SD of triplicate determinations. B2C10 inhibits (*, $p < 0.001$) and A3A12 augments (**, $p < 0.0001$) galectin-3-induced superoxide production.

B2C10 was also found to abrogate the potentiating effect of MAb A1D6 on galectin-3 binding, as shown in Figure 4, panel C.

(4) Effect on the Neutrophil Stimulation Activity of Galectin-3. We have shown previously that galectin-3 can activate various cell types, probably through recognition and cross-linking of cell surface glycoproteins. We tested the effet of mAbs on the ability of galectin-3 to stimulate superoxide production by human neutrophils. As shown in Figure 5, mAb B2C10 inhibited the effect of galectin-3, while the isotype-matched control mAb (anti-DNP, IgG_1, 109.3) had a negligible effect. In contrast, mAb A3A12 significantly enhanced the galectin-3-induced superoxide production.

DISCUSSION

A major finding of this study is that all MAbs generated from mice immunized with the intact galectin-3 bound the amino-terminal region of this protein. In fact, the extreme amino-terminal residues appear to constitute a highly immunogenic "hot spot", since epitopes for all these MAbs were found to be within the first 45 amino acids of galectin-3. The structural basis for the high immunogenicity is unknown. However, it is probably related to the unique sequence of the amino-terminal region of the protein, which contains tandem repeats of Tyr-Pro-Gly-Gln(Pro)-Ala(Thr)-Pro(Ala)-Pro-Gly-Ala (Robertson et al., 1990). Previously we noted, in generating polyclonal antibodies to galectin-3, that the animals exhibited persistent high-titer antibody levels for several months after just two immunizations (unpublished observations). The unique tandem repeats in galectin-3 may render this protein, particularly the very amino-terminal portion, highly immunogenic, thus also contributing to the prolonged antibody response.

The finding that MAbs recognizing the non-lectin domain of galectin-3 modulate the lectin function of this protein is noteworthy. Many of the MAbs have potentiating activity in that they enhance (i) the binding of galectin-3 to IgE coated on microtiter wells (Figure 3), (ii) the hemagglutination activity of galectin-3, (iii) the binding of fluorescent-labeled galectin-3 to mammalian cell surfaces (Figure 4), and (iv) galectin-3-induced superoxide production from human neutrophils (Figure 5). These potentiating activities of the MAbs are probably due to the bridging of two or more galectin-3 molecules by the MAbs, resulting in complexes with enhanced avidities for multivalent ligands. This mechanism is supported by the control experiment in which the Fab′ fragment of MAb A3A12 failed to show any significant enhancement of galectin-3 binding to IgE-coated plates (Figure 3A, inset). Previously, we have reported that galectin-3 exhibits cooperativity in binding to IgE (Hsu et al., 1992) as well as to human neutrophil cell surface (Yamaoka et al., 1995) and proposed that these phenomena are due to the formation of galectin-3 dimers or oligomers through intermolecular interactions involving the amino-terminal region of the molecule (Hsu et al., 1992; Yamaoka et al., 1995). Our interpretation of the potentiating activities of the MAbs is consistent with this proposal in that the MAbs facilitate the formation of galectin-3 dimers or oligomers, which have enhanced activities over the monomers.

The inhibitory activity of MAb B2C10 is remarkable. It was clearly demonstrated in the assay for binding of galectin-3 to IgE (Figure 3), the hemagglutination assay, and galectin-3-induced superoxide production from neutrophils (Figure 5), but is less evident in the FACS analysis of the binding of FITC-labeled galectin-3 to HeLa cells (Figure 4). It is possible that galectin-3 binding to the HeLa cell surface involves higher affinity interactions than its binding to IgE or the neutrophil surface, and thus is more resistant to inhibition by the MAb. It is clear, however, that in the FACS analysis, MAb B2C10 inhibited the potentiating activity of another MAb, A1D6.

It is interesting that MAb B2C10, that inhibits the galectin-3 activities, apparently binds to the extreme amino-terminal end of galectin-3, while the carbohydrate-binding site (i.e., the site that is in direct contact with the oligosaccharides on IgE, erythrocytes, and mammalian cell surface proteins) resides in the carboxyl-terminal domain. We favor the explanation that this MAb inhibits the self-association process of galectin-3 that is required for the higher affinity interactions between galectin-3 and the relevant glycoproteins in the systems being investigated. Another possibility is that the MAb binds to the amino-terminal region but is able to sterically hinder carbohydrate binding in the carboxyl-terminal domain. This is less likely because two other MAbs (B1A7 and B3A12) that apparently bind the same region recognized by B2C10 do not have an inhibitory activity. It is interesting that MAbs with the same or nearby epitopes have opposite effects on the activity of galectin-3. One possible explanation is that some MAbs (e.g., A3A12) have a more flexible Fab structure and thus the two antigen-combining sites can bind the epitopes on two separate galectin-3 molecules, resulting in galectin-3 dimers, whereas other MAbs (e.g., B2C10) have more rigid and narrow-angled Fab and can only form one-to-one complexes with the antigen. Consequently, the latter type of MAb can sterically hinder the intermolecular interactions, thus preventing galectin-3 dimer or oligomer formation. Another possibility is that MAb B2C10 preferentially recognizes two separate sites on galectin-3 protein simultaneously, forming

a cyclic complex, and galectin-3 dimerization is prohibited by steric hindrance.

In summary, we have generated a number of anti-galectin-3 MAbs exhibiting properties with interesting mechanistic implications. The extreme amino-terminal part of galectin-3 appears to be the immunologically dominant domain in that epitopes for all the MAbs obtained from mice immunized with the intact galectin-3 reside in the first 45 amino acids. Although the MAbs bind the non-lectin domain, they are capable of influencing the lectin function of galectin-3. This is probably related to the previously demonstrated self-association property of galectin-3, which is critically dependent on the amino-terminal region. These MAbs should be useful for further structural and functional analyses of galectin-3.

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Project 2: "Galectins In Pathogenesis Of Asthma: Chemotactic Effects"
Principal Investigator: Fu-Tong Liu

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"Validation of galectin-3 as a target in cancer therapy"
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